UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,944	12/19/2001	T. Christian Boles	EXT-073 C1	8399

7590 03/27/2003

Hollie L. Baker
Hale and Dorr LLP
60 State Street
Boston, MA 02109

EXAMINER	
EINSMANN, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	12

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,944	BOLES ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-12,19,20,24,26,29,30,40,42-44 and 50* is/are pending in the application.

4a) Of the above claim(s) *44 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10-12,19,20,24,26,29,30 and 40* is/are rejected.

7)☒ Claim(s) *42, 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☒ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 9/24/02, paper number 6. The inclusion of the paragraph making the previous office action final was an inadvertent error on the part of the examiner in light of the fact that new grounds of rejection were raised in the first office action on the continuation application. Thus, the finality of the previous office action is hereby WITHDRAWN. The amendments set forth in paper number 6 have been entered. The notice of appeal filed 9/24/02 is thus moot, and the appeal is hereby DISMISSED.

2. Claims 1, 2, 4, 5, 8, 10, 19-24, 26, 29-30, 40, 42, and 43 have been amended. Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42-44, and 50 are pending. Claims 44 and 50 are withdrawn from prosecution. Applicant's amendments and arguments have been thoroughly reviewed, but are not sufficient to place the claims in condition for allowance for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Election/Restrictions

3. Applicant's election of group I in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This rejection applies to claim 40 insofar as it would require SRP RNA from organisms belonging to specifically listed genuses of protozoa, fungi and bacteria. The practice of this invention requires knowledge of the specific sequences of the SRP RNA of these organisms in order to design probes for use in their detection. The specification does not provide specific disclosure of the sequences of SRP RNA for these genuses, and further, these sequences would not have been known to one of ordinary skill in the art at the time the invention was made because Zwieb et al. (Nucleic Acids Research, 2000, Vol. 28, No. 1 (171-172)) teach all known SRP RNA sequences and these species are not included in their database. Furthermore and extensive search of commercial databases revealed that these sequences are not disclosed in the prior art. As such, the specification lacks sufficient written description of the claimed invention. The examiner is aware that the SRP RNA sequences for some of the claimed genuses are

available in the prior art (*Bacillus*, *Pseudomonas, Chlamydia, Chlostridia, Escherichia, Helicobacter, Legionella, Haemophilus*, *Trypanosoma,* and *Ureaplasma*), and these are considered to have met the written description requirement. This rejection applies to claim 40 with regard to those groups claimed for which there has been no disclosure of the appropriate nucleic acid sequences either in the instant specification or in the prior art.

New Grounds of Rejection, Necessitated by Applicant's Amendments

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "wherein the immobilized nucleic acid probe(s) comprise(s) a detectable moiety" in claims 2 and 5 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the

specification by the examiner find any basis for the limitation. The specification at page 6, lines 14-26 talk about a sample, a gel-immobilized probe, and a third nucleic acid probe. The specification teaches that the sample or the "nucleic acid probe" may be labeled, but the specification does not appear to teach that the gel immobilized probe can be labeled. Furthermore, the specification does not describe how a method wherein the gel immobilized probes were labeled would work since it is unclear how to detect hybridization if all of the probes immobilized in the solid support are labeled. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 103

8. Claims 1, 4, 8, 10, 12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of both Nakamura et al. (Nucleic Acids Research 20(19): 5227-5228) and Jiro *et al.* (Japanese Unexamined Patent Application Number H3[1991]-47097) .

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to

the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Nakamura et al. teach sequence of the SRP RNA (the scRNA) for ten species of *Bacillus*, and further provide an alignment of these sequences (see Fig. 1). Nakamura et al. point out that there is a block containing complete primary sequence identity which corresponds to nucleotides 154-175 of the *B. subtilis* scRNA (p. 5227). Instantly disclosed SEQ ID NO: 2 consists of the complement of nucleotides 154-175 of the *B. subtilis* sequence, and instantly disclosed SEQ ID NO: 3, 4 , and 5 are smaller portions of this region. Instant SEQ ID NO: 25 is identical to

nucleotides 151-163 of the B. thurigiensis scRNA taught by Nakamura *et al.* and instant SEQ ID NO: 24 is identical to nucleotides 151-163 of the B. brevis sequence (numbering according to the B. subtilis sequence).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have probes comprising the SRP RNA taught by Nakamura et al. in the detection method taught by Hogan et al. In light of the teachings of Nakamura et al. which specifically point to a region of the SRP RNA that is conserved among Bacillus species and demonstrates via the alignment regions of the genome that are particular to different Bacillus species, and the clear teachings on probe selection and the use of nucleic acid probes provided by Hogan et al., the ordinary practitioner would have been motivated to select probes from the 21 base pair conserved region of the *Bacillus* genome in order to have created a rapid and effective method for detecting *Bacillus*. Additionally, the ordinary practitioner would have been motivated to select probes from outside of this conserved region to develop species specific probes, since Hogan *et al.* also provide guidance as to how to make species specific probes. One would be motivated to detect *Bacillus* in a sample, and particularly a human sample since some species of *Bacillus* are pathogenic to humans, for example *B. cereus*. The combination of the teachings of Hogan et al. with those of Nakamura et al. would have resulted in a rapid and effective method for detecting *Bacillus* in a sample.

The method taught by Hogan *et al.* in view of Nakamura *et al.* does not teach the steps of

introducing the sample comprising SRP RNA into an electrophoretic medium comprising an immobilized nucleic acid probe, nor do they teach subjecting the electrophoretic medium to an electric field such that the immobilized nucleic acid probe hybridizes to SRP RNA.

Jiro *et al.* teach methods for hybridization assays in which a nucleic acid probe is fixed within an electrophoretic carrier and a nucleic acid sample is made to move within the carrier by means of electrophoresis (p. 2 of the translation, claim 1). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Hogan *et al.* in view of Nakamura *et al.* so as to have immobilized the nucleic probes into an electrophoretic carrier and to have subjected the electrophoretic medium to an electric field so that the sample migrates through the medium and the immobilized nucleic acids. One would have been motivated to modify the methods taught by Hogan *et al.* in view of Nakamura *et al.* in this way in order to take advantage of the benefits of the methods disclosed by Jiro *et al.* since Jiro *et al.* specifically teach "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly and the reaction to be completed in a shorter time than would be the case were it to undergo passive diffusion...(p. 11 of the translation)."

9. Claims 1, 4, 8, 10-12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view Griffin (Journal of Biological Chemistry (1975) 250(14):5426-5437) and Jiro *et al.* (Japanese Unexamined Patent Application Number H3[1991]-47097) .

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Griffin teaches sequence of 4.5 S RNA from *E. coli* (Abstract, Fig. 10) and that the 4.5 S RNA has been shown to be a component of a number of strains of E. coli. Instant SEQ ID NO: 6 consists of the complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the complement of nucleotides 40-52, and instant SEQ ID NO: 9 of the complement of nucleotides 65-82. Therefore, the 110 base pair RNA disclosed by Griffin comprises instant SEQ ID NO: 6, 22, and 9.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have selected probes from the 4.5 S RNA taught by Griffin for the detection of E. coli in the methods taught by Hogan et al. in order to have created a method for the detection of E. coli. The ordinary practitioner would have been motivated to have used the SRP RNA because Griffin teaches that this RNA has been shown to be a component of a number of strains of E. coli, and Hogan *et al.* teach methods for the detection of non-viral organisms which utilize probes to conserved RNA sequences in the target organism. Furthermore, the ordinary practitioner would have been motivated to detect E. coli in a sample, including a human sample, because some E. coli are pathogenic to humans.

The method taught by Hogan *et al.* in view of Griffin *et al.* does not teach the steps of introducing the sample comprising SRP RNA into an electrophoretic medium comprising an immobilized nucleic acid probe, nor do they teach subjecting the electrophoretic medium to an electric field such that the immobilized nucleic acid probe hybridizes to SRP RNA.

Jiro *et al.* teach methods for hybridization assays in which a nucleic acid probe is fixed within an electrophoretic carrier and a nucleic acid sample is made to move within the carrier by means of electrophoresis (p. 2 of the translation, claim 1). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Hogan *et al.* in view of Griffin *et al.* so as to have immobilized the nucleic probes into an electrophoretic carrier and to have subjected the electrophoretic medium to an electric field so that the sample migrates through the medium and the immobilized nucleic acids. One would have been motivated to modify the methods taught by Hogan *et al.* in view of Griffin *et al.* in this way in order to take advantage of the benefits of the methods disclosed by Jiro *et al.* since Jiro *et al.* specifically teach "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly and the reaction to be completed in a shorter time than would be the case were it to undergo passive diffusion...(p. 11 of the translation)."

10. Claims 1, 4, 8, 10-12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Larsen et al. (Nucleic Acids Research 19(2) 209-215) and Jiro *et al.* (Japanese Unexamined Patent Application Number H3[1991]-47097).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the

hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Larsen et al. teach the sequences of SRP RNA from 39 species of organisms, including the 4.5S RNA of E. coli. Instant SEQ ID NO: 6 consists of the complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the complement of SEQ ID NO: 65-82. Therefore, the E. coli

RNA disclosed by Larsen et al. comprises instant SEQ ID NO: 6, 22, and 9. Larsen et al. also teach the SRP RNA sequence from a fungus, specifically, the yeast *Schizosaccaromyces pombe.*

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the alignment provided by Larsen et al. and the clear instructions on probe selection provided by Hogan et al. in order to have selected probes useful in the methods taught by Hogan et al. for the detection of any one of the species disclosed by Larsen et al. It would have been further obvious to have used such probes to detect, for example, E. coli in humans since E. coli is a pathogen to humans. An ordinary practitioner would have been motivated to develop such a detection assay in order to have provided a rapid method for screening for pathogens in samples.

The method taught by Hogan *et al.* in view of Larsen *et al.* does not teach the steps of introducing the sample comprising SRP RNA into an electrophoretic medium comprising an immobilized nucleic acid probe, nor do they teach subjecting the electrophoretic medium to an electric field such that the immobilized nucleic acid probe hybridizes to SRP RNA.

Jiro *et al.* teach methods for hybridization assays in which a nucleic acid probe is fixed within an electrophoretic carrier and a nucleic acid sample is made to move within the carrier by means of electrophoresis (p. 2 of the translation, claim 1). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Hogan *et al.* in view of Larsen *et al.* so as to have immobilized the nucleic probes into an electrophoretic carrier and to have subjected the electrophoretic medium to an electric field so that the sample migrates through the medium and the immobilized nucleic acids.

One would have been motivated to modify the methods taught by Hogan *et al.* in view of Larsen *et al.* in this way in order to take advantage of the benefits of the methods disclosed by Jiro *et al.* since Jiro *et al.* specifically teach "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly and the reaction to be completed in a shorter time than would be the case were it to undergo passive diffusion...(p. 11 of the translation)."

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10, 12, and 19 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10-12, and 19 above, and further in view of Rudert et al.

(C) Hogan *et al.* in view of Larsen et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10-12, and 19 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as discussed in the previous rejections. These teachings do not teach methods in which the SRP RNA is labeled.

Rudert et al. teach that the reverse dot blot technique is useful for detecting nucleic acid sequences, and that in this technique sample nucleic acids are labeled and hybridized to probes bound to a solid support (Col. 3, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to labeled the SRP RNA for use in the methods taught by A-C. An ordinary practitioner would have been motivated to label the SRP RNA for use in the methods taught by A-C in order to have enabled the visualization of the hybridized sample to the immobilized detection probes as is exemplified by Rudert *et al.*

12. Claims 20, 24, 29-30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Nakamura et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10, 12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Nakamura et al. in view of Jiro *et al.* are applied to this rejection as discussed in the previous rejections. Hogan et al. in view of Nakamura et al. in view of Jiro *et al.* do not teach a method in which a duplex SRP RNA is contacted with a gel immobilized probe in a capture assay. However, such capture assays were routine in the prior art at the time the invention was made. For example, Gosh *et al.* teach contacting a duplex with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Nakamura *et al.* in view of Hogan *et al.* in view of Jiro *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53), and thus the combination of the methods of the prior art would have led to an alternative and effective methodology for the detection of non-viral organisms in a sample.

13. Claims 20, 24, 30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Griffin et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10-12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Griffin et al. in view of Jiro *et al.* are applied to this rejection as discussed in the previous rejections. Hogan et al. in view of Griffin et al. in view of Jiro *et al.* do not teach a method in which a duplex SRP RNA is contacted with a gel immobilized probe in a capture assay. However, such capture assays were routine in the prior art at the time the invention was made. For example, Gosh *et al.* teach contacting a duplex with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Griffin *et al.* in view of Hogan *et al.* in view of Jiro *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53), and thus the combination of the methods of the prior art would have led to an alternative and effective methodology for the detection of non-viral organisms in a sample.

14. Claims 20, 24, 29-30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Larsen et al. and Jiro *et al.* as applied to claims 1, 4, 8, 10-12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Larsen et al. in view of Jiro *et al.* are applied to this rejection as discussed in the previous rejections. Hogan et al. in view of Larsen et al. in view of Jiro *et al.* do not teach a method in which a duplex SRP RNA is contacted with a gel immobilized probe in a capture assay. However, such capture assays were routine in the prior art

at the time the invention was made. For example, Gosh *et al.* teach contacting a duplex with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Larsen *et al.* in view of Hogan *et al.* in view of Jiro *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid

supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53), and thus the combination of the methods of the prior art would have led to an alternative and effective methodology for the detection of non-viral organisms in a sample.

15. Claims 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura *et al.* and Jiro *et al.*, and further in view of Ghosh *et al.* as applied to claims 20, 24, 29-30, and 40 above, and further in view of Urdea et al.

(B) Hogan et al. in view of Griffin et al. and Jiro *et al.*, and further in view of Ghosh *et al.* as applied to claims 20, 24, 30, and 40 above, and further in view of Urdea et al.

(C) Hogan et al. in view of Larsen et al. and Jiro *et al.*, and further in view of Ghosh *et al.* as applied to claims 20, 24, 29-30, and 40 above, and further in view of Urdea et al.

The teachings of all of the above combinations are applied to this rejection previously stated. These teachings do not teach methods in which the nucleic acid probe is an adaptor probe comprising a subsequence of that hybridizes to the gel-immobilized probe.

Urdea et al. teach nucleic acid sandwich assays which utilize an adaptor probe which has regions that hybridize to both the sample and the immobilized probe (Col. 1, lines 50-53).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the probe taught by Urdea et al. in any one of the methods

taught by A-C in order to have provided a more efficient capture based detection method since Urdea et al. teach that such a method is advantageous because "using combinations of nucleic acid sequences complementary to a nucleic acid analyte and to arbitrary sequences and specific binding pair members, a detectable label may be separated in two phases in proportion to he amount of analyte present in the sample (Col. 2, lines 29-24)."

Response to Remarks

The previously set forth rejections under 112 2nd paragraph have been withdrawn in view of applicant's amendments to the claims.

The rejection of claim 40 under 112 1st paragraph for lack of written description is maintained. Applicant submits that the proper standard for 112 1st paragraph is whether one skilled in the art could make and use the invention without undue experimentation based on the disclosure in the patent application coupled with information known in the art. However, this is not persusive because the standard to which applicant refers is the standard for enablement of the claims under 112 1st paragraph, not the standard for assessing written description. The court has made it clear that with regard to chemical compounds, the standard for written description is possession, not enablement or intent to claim. "While we have no doubt a person so motivated would be enabled by the specification to make it, this is beside the point for the question is not whether he would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. We think it does not." In Re Ruschig, 379 F.2d 990, 995, 154 U.S.P.Q. 118, 123 (CCPA 1967). Furthermore, the court stated "Accordingly, naming a type of material generally known to exist, in the absence of knowledge

as to what that material consists of, is not a description of that material." The Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q.2d 1406 (Federal Circuit 1997). In the instant case, although applicant have not provided the nucleic acid sequences essential for the practice of the claimed invention with regard to all of the non-viral species of organisms listed in claim 40. Thus, the rejection is maintained.

The arguments concerning the rejections in view of the prior art are moot in view of the new grounds of rejection set forth herein.

Allowable Subject Matter

16. Claims 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 42 and 43 are free of the prior art because SEQ ID NO: 7 and 8, one of which is required for the claims, are free of the prior art. These sequences are "adaptor probes" comprising a sequence specific for the target SRP RNA and an arbitrary sequence specific for a capture probe. While Urdea *et al.* describes such adaptor probes, Urdea *et al.* does not provide the specific sequence of the adaptor portion of SEQ ID NO: 7 and 8. These adaptor sequences are not provided in the prior art.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The complement of instant SEQ ID NO: 11 consists of the complement of nucleotides is contained in the disclosure of E. coli 4.5 S RNA by Hsu *et al.* (J. Mol. Biol. (1984)

178(3) 509-31). Rejections utilizing these reference would have been duplicative of those rejections already of record.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C Einsmann
Examiner
Art Unit 1634

March 25, 2003